DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 30 June 2011 has been entered.

Status of the Claims

2. Claims 16-28 are pending in the present application. Claims 25-28 are withdrawn as being directed to a nonelected invention. Therefore, claims 16-24 are examined herein on the merits for patentability. No claim is allowed at this time.

Withdrawn Rejections

3. Rejections and/or objections not reiterated from the previous Office Action are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set of rejections and/or objections presently being applied to the instant application.

Claim Rejections - 35 USC § 102

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

5. Claims 16-18, 20, 21 and 24 are rejected under 35 U.S.C. 102(b) as being anticipated by Mifune et al. (US 3,846,551).

Mifune et al. disclose compositions comprising a pyrethroid with a cyclodextrin which contributes to the improvement of the stability of the pyrethroids to heat and light and exhibits insecticidal and acaricidal effects (col. 1, ln. 4-10). Mifune et al. further disclose that the cyclodextrins available are α-cyclodextrin, β-cyclodextrin, and γ-cyclodextrin (col. 3, ln. 52-59). Mifune et al. disclose that the active ingredient can be formed by contacting at least one pyrethroid intimately with at least one cyclodextrin in the presence of water, it will be readily understood that depending upon the formulation, the interacted product can be formed at the time of preparing the final pesticidal composition instead of preparing the interacted product in advance and then blending it with a diluent or carrier. For instance, in the case of a wettable powder, the interacted product can be formed during its preparation (col. 5, ln. 27-37).

The insecticidal and acaricidal composition of Mifune et al. may be in various formulations, such as a liquid, emulsifiable concentrate, wettable powder, oil, aerosol, paste, fumigant, dust, granule, tablet, or pellet (col. 5, ln. 38-41). The insecticidal and acaricidal composition contains various gaseous, liquid or solid diluents or carriers, and

if desired, may be further contain various assistants, such as a surface active agent, emulsifier, dispersing agent, spreader, sticker, synergist, antioxidant, ultraviolet absorbent, and other insecticide (col. 5, ln. 43-49), wherein examples of the synergist include piperonyl butoxide (col. 6, ln. 32).

Mifune et al. further disclose examples wherein a pyrethroid, cyclodextrin and piperonyl butoxide are well kneaded to form a paste (Formulation Example 7). Cyclodextrin complexes are known to form by kneading with other components, such as pyrethroids and synergists (col. 4, ln. 1-19). The proportions of the pyrethroid to the cyclodextrin in the resulting complex may vary over a range of 0.5 to 1.5 mols per mol of the cyclodextrin (col. 4, ln. 26-29). Therefore, the compositions according to Formulation Example 7 would comprise both the pyrethroid and the synergist complexed with cyclodextrin since they were well kneaded in the presence of cyclodextrin in water.

Response to Arguments

Applicant argues that Mifune et al. describe the complexation between the insecticide and a cyclodextrin, but nowhere is joint complexation also with a synergistic compound disclosed. Mifune et al. states that the preformed interacted compound of pyrethroid and beta-cyclodextrin is mixed with PBO, stearic acid, Tween 60 and Span 60. The complex therefore which is already formed is made by the pyrethroid and the cyclodextrin. The kneading of this pre-formed complex with excipients and PBO lead to a paste formulation. However, the presence of all such ingredients make it very *unlikely* that the PBO is included in the cyclodextrin cavity, even more so considering that the

cavities are already occupied by the pyrethroid. Applicant further argues that while kneading is a known method for preparing an inclusion complex, in order to be effective it needs particular operative conditions in terms of time, temperature and component ratios which are not the same as those required by the kneading for the mere purpose of preparing a paste formulation.

However, the examiner respectfully argues that Mifune et al. disclose mixing an interacted compound of furamethrin and β-cyclodextrin, PBO, stearic acid, SPAN 60, Tween 60, and water, wherein the mixture is well kneaded (Formulation Example 7). Mifune et al. disclose sufficiently kneading the active with cyclodextrin and water in a kneader to prepare a cyclodextrin complex, wherein the suitable temperature range is 5-70 ℃, and usually the kneading is carried out for about 30 minutes (col. 4, ln. 1-19). Therefore, it is the position of the examiner that kneading a mixture of an interacted compound of furamethrin and β-cyclodextrin with PBO in water will result in jointly complexing both the furamethrin and PBO with the CD.

The arguments of counsel cannot take the place of evidence in the record. *In re Schulze*, 346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965). Examples of attorney statements which are not evidence and which must be supported by an appropriate affidavit or declaration include statements regarding unexpected results, commercial success, solution of a long-felt need, inoperability of the prior art, invention before the date of the reference, and allegations that the author(s) of the prior art derived the disclosed subject matter from the applicant. See MPEP 716.01(c)(II). Therefore,

absent evidence to the contrary, the examiner respectfully argues that Mifune et al. disclose jointly complexing both furamethrin and PBO with CD.

Applicant further argues that even assuming that a CD complex is formed under the conditions referred to in Example 7, this complex would have incorporated in its cavity not only the pyrethroid but also the additional kneaded ingredients, that is stearic acid, Tween 60, Span 60 and PBO.

The examiner respectfully argues that the instant claims do not preclude the presence of other components in the CD complex, but rather state that the composition *comprises* the active principle and synergist jointly complexed with CD. Therefore, even if other ingredients were incorporated into the cavities of the CD, the complex would still fall within the scope of the instant claims.

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. The factual inquiries set forth in Graham v. John Deere Co., 383 U.S. 1,148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.

4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

8. Claims 16-24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Biebel et al. (International Journal of Pharmaceutics, 2003) and Szejtli et al. (US 4,524,068).

Determination of the scope and content of the prior art

(MPEP 2141.01)

Biebel et al. teach that pyrethrum extract is an ideal pesticide, but it has low light stability (Abstract; and pg. 175, Introduction). This drawback can be overcome by the complexation of pyrethrum extract with γ-cyclodextrin (Abstract; pg. 176, sentence bridging the left and right columns; and section 2.2.1). Biebel et al. further teach that pyrethrins, such as pyrethrum extract, experience rapid metabolism which is a drawback concerning the frequency of application. Therefore, synergists are added to ensure an insecticidal effect or pyrethrum, wherein the most widely used synergist in the last decades has been piperonyl butoxide (PBO) (pg. 175, right column, ln. 2-12). Biebel et al. teach that synergists may also profit from a complexation with cyclodextrins, and thus sesamol was also complexed with γ-cyclodextrin (pg. 176, right column, ln. 2-7; and section 2.2.2). Biebel et al. teach compositions comprising a 10 to 50 fold excess synergist compared to pyrethrum (Table 1).

Szejtli et al. teach that numerous efficient insecticidal active ingredients are decomposed by the mitochondrial non-specific oxidative enzymes of the insects so rapidly that the exerted effect is very low. The synergistic effect of piperonyl butoxide and other similar synergistic components manifests itself in the fact that the said agent

inhibits the rapid inactivation of the active ingredient by the oxidase enzymes of mixed function. The said synergistic agents are useful not only in combination with insecticides but also with fungicides and they are capable of increasing the effect of the active ingredient by ten to fifty times (col. 1, ln. 15-25).

Szejtli et al. teach that piperonyl butoxide is generally used to synergize pyrethrins and synthetic pyrethroids and organic phosphate compositions. Studies relating to the relationship between the synergistic effect and chemical structure of piperonyl butoxide (referred to further on as "PBO") have shown that the methylenedioxy phenyl group is the most important functional moiety of the molecule and that any modification or change of the said group leads to the complete loss or strong reduction of the synergistic activity (col. 1, ln. 34-43).

Szejtli et al. further teach that it is known that the active ingredients of drugs and pesticides can be included into cyclodextrins and the inclusion complexes thus obtained can influence and modify the biological characteristics thereof. It has been found that the solubility of piperonyl butoxide (PBO) and other similar synergistic agents can be increased by forming a cyclodextrin complex. The inclusion complex goes into solution more rapidly and thereby the velocity of penetration through the biological membrane is increased as well. The absolute activity of the synergistic component becomes higher and therefore in an identical active ingredient concentration the biological effect is exhibited more promptly and stronger or the same biological effect can be reached by using a lower active ingredient concentration (col. 1, ln. 59 through col. 2, ln. 6).

Szejtli et al. teach that the advantages of the piperonyl butoxide-cyclodextrin inclusion complex over the piperonyl butoxide molecule can be summarized as follows: (1) the inclusion complexes are solid crystalline products, which can be easily handled and readily formulated; (2) the amount of piperonyl butoxide which can be dissolved from the inclusion complex is by 2.5 to 4 times larger than the amount of pure piperonyl butoxide dissolved in aqueous solution; (3) as a result of the higher water solubility the absorption of the synergistic agent is increased and the velocity of penetration through the biological membrane becomes larger and consequently the absolute concentration of the active ingredient increases as well; and (4) as a consequence of the aforesaid when using identical active ingredient concentration the biological effect is quicker and stronger and an identical active biological effect can be achieved with the aid of a lower active ingredient concentration (col. 2, ln. 30-49).

The piperonyl butoxide-cyclodextrin inclusion complex can replace the original synergistic agent in insecticidal or fungicidal combinations to synergize the activity of pyrethrins, synthetic pyrethroids or organophosphates (col. 2, ln. 50-55).

Ascertainment of the difference between the prior art and the claims

(MPEP 2141.02)

Biebel et al. and Szejtli et al. do not explicitly disclose jointly complexing the pyrethrin or pyrethroid and the synergist with cyclodextrin, as instantly claimed. However, Biebel et al. teach complexation of pyrethrum extract with γ-cyclodextrin, and also teach that synergists may also profit from a complexation with cyclodextrins. Szejtli et al. teach that it is known that the active ingredients of drugs and pesticides can be

included into cyclodextrins and the inclusion complexes thus obtained can influence and modify the biological characteristics thereof. It has been found that the solubility of piperonyl butoxide (PBO) and other similar synergistic agents can be increased by forming a cyclodextrin complex. The inclusion complex goes into solution more rapidly and thereby the velocity of penetration through the biological membrane is increased as well. The absolute activity of the synergistic component becomes higher and therefore in an identical active ingredient concentration the biological effect is exhibited more promptly and stronger or the same biological effect can be reached by using a lower active ingredient concentration. Therefore, Biebel et al. and Szejtli et al. clearly teach the benefits of forming inclusion complexes of pyrethrins or pyrethroids in cyclodextrin, as well as the benefits of forming inclusion complexes of synergists such as PBO in cyclodextrin.

Finding of prima facie obviousness

Rational and Motivation (MPEP 2142-43)

Therefore, it would have been *prima facie* obvious for one of ordinary skill in the art at the time of the invention to form an inclusion complex of both pyrethrins or pyrethroids and synergist in a cyclodextrin, with the reasonable expectation that inclusion of the pyrethrin or pyrethroid will increase its bioefficacy, and inclusion of the synergist will increase its solubility as well as synergistically increasing the bioefficacy of the pyrethrin or pyrethroid.

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed

invention. Therefore, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Response to Arguments

Applicant argues that the teachings of Biebel et al. may suggest, at most, to one of ordinary skill in the art how to arrive at a mixture of pyrethroid/CD complex with a synergist/CD complex; which is decidedly different and readily distinguishable from the claimed double inclusion complex. Applicant further argues that Biebel et al. teach that the pyrethrum/CD complex + PBO showed practically the same efficiency as the mixture of pyrethrum and PBO, both without CD.

The examiner respectfully argues that, as discussed above, one of ordinary skill in the art would reasonably expect an inclusion complex of both pyrethrins or pyrethroids and synergist in a cyclodextrin to synergistically increasing the bioefficacy of the pyrethrin or pyrethroid. Also, Biebel et al. teach that complexation of pyrethrum extract with CD had a small enhancing effect on insect death, which can be recognized on the second day.

Applicant also argues that the entirely unexpected improvement in insecticidal effectiveness of the claimed complexed composition is strictly due and connected to the differential release of the two components, with a sustained release for the active pyrethroid of the complex and an earlier and fast release of the PBO component. The earlier/fast release of the PBO inhibits the detoxification enzymes of the insects, while

the sustained release of the pyrethroids exerts an action on the insects which have been pre-sensitized by PBO providing a synergistic disinfestation.

The examiner respectfully argues that Szejtli et al. teach that the synergistic effect of PBO and other similar synergists on insecticidal active ingredients manifests itself in the fact that the said synergistic agents inhibit the rapid inactivation of the active ingredient by the oxidase enzymes of mixed function (col. 1, ln. 15-25). Szejtli et al. further teach that the solubility of PBO and other similar synergistic agents can be increased by forming a cyclodextrin complex; and the inclusion complex goes into solution more rapidly and thereby the velocity of penetration through the biological membrane is increased as well. The absolute activity of the synergistic component becomes higher and therefore in an identical active ingredient concentration the biological effect is exhibited more promptly and stronger or the same biological effect can be reached by using a lower active ingredient concentration (col. 1, ln. 64 to col. 2, ln. 6). Therefore, Szejtli et al. teach that the synergist works because it inhibits the inactivation of the active ingredient by oxidase enzymes, and the effect is enhanced when the PBO is complexed with cyclodextrin. Thus, it is not unexpected that including PBO in the CD complex with the pyrethroid also leads to a synergistic enhancement of the pyrethroid by inhibiting the oxidase enzymes.

Contact Information

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nathan W. Schlientz whose telephone number is

(571)272-9924. The examiner can normally be reached on 9:00 AM to 5:30 PM, Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Johann R. Richter can be reached on 571-272-0646. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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